on the nucleotide sequence of the human MI gene (Example 3; Figure 2 (SEQ ID NO: 9)).

Please replace the Sequence Listing filed August 29, 2001, with the enclosed Substitute Sequence Listing.

**IN THE CLAIMS:**

Please amend claim 53, as follows:

53. (Twice Amended) An isolated and purified antibody, wherein said antibody binds specifically to a polypeptide comprising an amino acid sequence SEQ ID NO: 7 or SEQ ID NO: 9.

**IN THE DRAWINGS:**

Subject to the approval of the Examiner, please replace Figures 1, 2, and 9 with the enclosed amended figures. Redlined copies of Figures 1, 2, and 9 showing the amendments are enclosed.

**REMARKS**

In the Communication mailed December 24, 2002, the Office states that this application fails to comply with the requirements of 37 C.F.R. § 1.821(a)(2)(c-d). Specifically, the Office indicates that pages 5-6 (for Figs. 1-2, and 9), 34-35, 37-39, 41, 43-44, 53, 57, and 56 and claim 53 do not include sequence identifiers.

Applicants have amended the specification and claim 53 to include sequence identifiers where appropriate. Applicants have also prepared paper and computer-readable versions of a Substitute Sequence Listing, which adds sequence identifiers 6-36 corresponding to protein and nucleic acid sequences disclosed in the application as filed.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

In connection with the Substitute Sequence Listing submitted concurrently herewith, the undersigned hereby states that:

1. the submission does not include new matter;

2. the content of the written Substitute Sequence Listing and of the computer readable copy of the Substitute Sequence Listing are the same; and

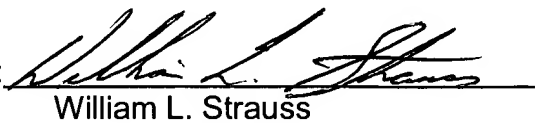
3. all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 20, 2003

By: 
William L. Strauss
Reg. No. 47,114

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Application Number: 08/803,954
Filing Date: August 29, 2001
Attorney Docket Number: 06843.0009-08

**APPENDIX TO AMENDMENT OF FEBRUARY 20, 2003**

**Version with Markings to Show Changes Made**

Amendments to the Specification (Additions shown by double underlining)

Paragraph beginning at line 20 on page 5:

--Figure 1 shows the cDNA sequence (SEQ ID NO: 6) and amino acid sequence (SEQ ID NO: 7) of bovine metalloproteinase inhibitor.--

Paragraph beginning at line 23 on page 5:

--Figure 2 shows the cDNA sequence (SEQ ID NO: 8) and amino acid sequence (SEQ ID NO: 9) of human metalloproteinase inhibitor.--

Paragraph beginning at line 16 on page 6:

--Figure 9 shows a synthetic DNA fragment (SEQ ID NOs: 35 and 36) constructed for use in the expression of recombinant human metalloproteinase inhibitor in E. coli, containing a ribosome binding site, an initiation methionine codon and codons for the first 42 amino acids of the mature protein.--

Table 4 on page 34:

--Table 4

Amino-terminal sequence of bovine peak I-derived inhibitor

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Cys)- | Ser- | (Cys)- | Ser- | Pro- | Val- | His- | Pro- | Gln- | Gln- | Ala- | Phe- | (Cys)- |

| 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

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Asn-Ala-Asp-Ile-Val-Ile-Arg-Ala-Lys-Ala-Val-Asn-Lys-

27 28 29 30 31 32 33 34 35 36 37 38 39

Lys-Glu-Val-Asp-Ser-Gly-Asn-Asp-Ile-Tyr-Gly-Asn-Pro-

40 41 42 43 44 45

Ile-Lys-Arg-Ile-Gln-Tyr----- (SEQ ID NO: 10)--

Table 5 on page 35:

--Table 5

Amino-terminal sequence of bovine peak II-derived inhibitor

1 2 3 4 5 6 7 8 9 10 11 12 13

(Cys)-Thr-(Cys)-Val-Pro-Pro-His-Pro-Gln-Thr-Ala-Phe-(Cys)-

14 15 16 17 18 19 20 21 22 23 24 25 26

Asn-Ser-Asp-Val-Val-Ile-Arg-Ala-Lys-Phe-Val-Gly-Thr-

27 28 29 30 31 32 33 34 35 36 37 38 39

Ala-Glu-Val-(Asn)-Glu-Thr-Ala-Leu-Leu-Tyr-Arg-Tyr-Leu-

40 41 42 43 44 45 46 47 48 49

Ile-Lys-Met-[Leu]-Lys-Met-Pro-Ser-[Gly]-Phe--- (SEQ ID NO: 11)--

Table 6 on page 37:

Comparison of the amino-terminal sequence of (1) human TIMP[a], (2) bovine peak II-derived inhibitor (TIMP)[b] and (3) bovine peak I-derived inhibitor (MI)[c]

1 10 20

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| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 HUMAN TIMP | C | T | C | V | P | P | H | P | Q | T | A | F | C | N | S | D | L | V | I | R |
| 2.BOVINE TIMP | C | T | C | V | P | P | H | P | Q | T | A | F | C | N | S | D | V | V | I | R |
| 3 BOVINE MI | C | S | C | S | P | V | H | P | Q | Q | A | F | C | N | A | D | I | V | I | R |

| | 21 | | | | | | | | | 30 | | | | | | | | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 HUMAN TIMP | A | K | F | V | G | T | P | E | V | N | Q | T | T | L | Y | Q | R | Y | E | I |
| 2 BOVINE TIMP | A | K | F | V | G | T | A | E | V | N | E | T | A | L | L | Y | R | Y | L | I |
| 3.BOVINE MI | A | K | A | V | N | K | K | E | V | D | S | G | N | D | I | Y | G | N | P | I |

| | 41 | | | | | | | | 49 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 HUMAN TIMP | K | M | | T | | K | M | Y | K | G | F (SEQ ID NO: 12) |
| 2 BOVINE TIMP | K | M | (L) | K | M | P | S | (G) | F | ... | (SEQ ID NO: 13) |
| 3 BOVINE MI | K | R | | I | | Q | Y | (SEQ ID NO: 14) | | | |

---

[a] From Docherty et al., Nature, supra: and Carmichael et al., Proc. Natl. Acad. Sci. USA, supra.
[b,c] From sequence analyses described in Example 2.--

Paragraph on page 37, line 25:

--The amino acid composition of the bovine peak I-derived inhibitor (MI) is shown in Table 7. A sample of the peak I-derived inhibitor (1.2 ml; Table 1, step 2.1.3) was concentrated and introduced into 50 mM ammonium bicarbonate, pH 7.8 using an Amicon Centricon 10 ultrafiltration unit. The sample was then dried and subjected to amino acid composition analysis by the method described by Lu et al. (J. Chromatog. 368, 215-231 (1986)). This involved chromatographic analysis of phenyltiocarbamyl-amino acids generated after acid hydrolysis (24 h) of the samples. Data from three

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202.408.4000
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separate chromatographic analyses were used to estimate average residues per molecule values. For each of these analyses an amount of material derived from one-tenth of the starting sample was used. The value for total amino acids (178) used in calculating residues per molecule was taken from the gene-encoded sequence for the mature bovine MI (Example 3, Figure 1 (SEQ ID NO: 7)).--

Paragraph on page 39, line 17:

--5′ GAT CAC AAT GTC AGC ATT GCA GAA GGC CTG CTG GGG ATG CAC AGG 3′ (SEQ ID NO: 15)--

Please replace the paragraph beginning at line 24 on page 39 with the following amended paragraph:

```
--          (T)   (T)   (T)                (T)
5′ GTC IAC (C)TC (C)TT (C)TT GTT IAC IGC (C)TT IGC 3′
```
(SEQ ID NO: 16)--

Paragraph beginning at line 32 on page 39:

```
--                  (A)       (A)       (A)   (A)
     5′ CTT IAT IGG (G)TT ICC (G)TA IAT (G)TC (G)TT ICC 3′
```
(SEQ ID NO: 17)--

The four paragraphs beginning at line 22 on page 41:

--probe 1
5′ CGG GTC CTC GAT GTC CAG AAA CTC CTG CTT GGG GGG TGC TGC TCC GCG GTA 3′ (SEQ ID NO: 18)

probe 2

5′ GAA CTT GGC CTG GTG TCC GTT GAT GTT CTT CTC CGT GAC GTC CAT CCA 3′ (SEQ ID NO: 19)

probe 3

5′ CGC CTC ACA GCC CAT CTG GTA CCT GTG GTT CAG GCT CTT CTT

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CTG GGT GGC 3′ (SEQ ID NO: 20)

probe 4

5′ GGG GTT GCC GTA GAT GTC GTT GCC AGA GTC CTC CTT CTT
ATT GAC TGC 3′ (SEQ ID NO: 21)--

Paragraph beginning at line 27 on page 43:

--ClaI KpnI
5′ CGATTTGATTCTAGAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC 3′
(SEQ ID NO: 22)
3′ TAAACTAAGATCTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGC 5′
(SEQ ID NO: 23)--

Paragraph beginning at line 1 on page 44:

--The pL DNA sequence inserted is as follows:

AatII
5′ CTAATTCCGCTCTCACCTACCAAACAATGCCCCCCTGCAAAAAATAAATTCATAT
3′ TGCAGATTAAGGCGAGAGTGGATGGTTTGTTACGGGGGGACGTTTTTTATTTAAGTATA

AAAAAACATACAGATAACCATCTGCGGTGATAAATTATCTCTGGCGGTGTTGACATAAA
TTTTTTGTATGTCTATTGGTAGACGCCACTATTTAATAGAGACCGCCACAACTGTATTT

TACCACTGGCGGTGATACTGAGCACAT 3′ (SEQ ID NO: 24)
ATGGTGACCGCCACTATGACTCGTGTAGC 5′ (SEQ ID NO: 25)

ClaI--

Paragraph beginning at line 26 on page 51:

--(ii) A GPD-α-factor linker

(Sau3A) met arg phe pro ser ile phe thr ala (SEQ ID NO: 26)
GATCACACATAAATAAACAAAATG AGA TTT CCT TCA ATT TTT ACT GCA (SEQ ID NO: 27)
TGTGTATTTATTTGTTTTAC TCT AAA GGA AGT TAA AAA TG (PstI) (SEQ ID NO: 28)--

Paragraph beginning at line 1 on page 52:

--(iv) A linker for joining the α-factor pre-pro leader to the α-factor terminator sequence such as:

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HindIII SphI SstI SmaI XhoI BglII (SalI)
AGCTTGCATGCGAGCTCCCCGGGCTCGAGATCTGATAACAACAGTGTAGATGTAACAAAA
(SEQ ID NO: 29)
ACGTACGCTCGAGGGGCCCGAGCTCTAGACTATTGTTGTCACATCTACATTGTTTTAGCT
(SEQ ID NO: 30)--

Paragraph beginning at line 1 on page 53:

--II. A polylinker, whose sequence is shown below, was inserted into a EcoRI site of the modified 2μ plasmid in (I) as shown in Figure 10(B.)

AATTC GATATC GAT GGTACC CGG GATCC GTCGAC AGATCT G (SEQ ID NO: 31)
G CTATAG CTA CCATGG GCC CTAGG CAGCTG TCTAGA CTTAA (SEQ ID NO: 32)
EcoRI EcoRV ClaI KpnI SmaI BamHI SalI BglII EcoRI--

Paragraph beginning at line 21 on page 57:

-- ClaI KpnI
5′ CGATTTGATTCTAGAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC 3′
(SEQ ID NO: 33)
3′ TAAACTAAGATCTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGC 5′
(SEQ ID NO: 34)--

Paragraph beginning at line 1 on page 66:

--A sample of this human MI preparation (about 27 μg) was subjected to amino-terminal amino acid sequencing through 20 cycles, using the methods described in Example 2. The initial yield was 923 pmol and the repetitive yield was 90-93%. The major sequence obtained exactly matched that predicted for mature human MI based on the nucleotide sequence of the human MI gene (Example 3; Figure 2 (SEQ ID NO: 9)).--

Amendments to the Claims

53. (Twice Amended) An isolated and purified antibody, wherein said antibody binds specifically to a polypeptide comprising an amino acid sequence [of FIG. 1 or in FIG. 2] SEQ ID NO: 7 or SEQ ID NO: 9.

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